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Protein Metabolism on Reduced Caloric and Water Intakes

SUMMARY

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GENERAL SUMMARY

The primary objective of these studies has been a clarification of the basic physiologic processes obtaining in human beings subjected to specific limitations in the intake of food and water.

This work was initiated in early 1945 under the guidance of Dr. C. G. King, Adviser to the Quartermaster General and Director of the Nutrition Foundation. It was at first projected simply as a brief, single testing on human beings of several proposed new rations for Army Air Corps Life Rafts. The results of these preliminary explorations, in conjunction with certain other findings brought to light by Major George Gelman, Technical Director of the Quartermaster Food and Container Institute, broadened the scope of our assignment, first toward improving the existing Life Raft Ration, then subsequently to encompass the problem of survival rations in general. These investigations were carried on in close liaison with other kindred groups working with the Institute, particularly those of Dr. Pearl Swanson at Iowa State College, and Dr. James B. Allison at Rutgers University, with all working closely under the coordinating direction of Dr. Samuel Lepkovsky.

Because of limitations on weight and space available in planes, the total Air Corps Life Raft Ration then consisted of only 100 grams of carbohydrate per man per day. Water was not stocked in the life rafts, since a castaway was expected to average a daily yield of 800 cc. from the combined use of the desalination kit, solar still, and rain water caught on a tarpaulin. In addition, the excellent physiological researches of Drs. James Gamble and Allan Butler had previously demonstrated that 100 grams of carbohydrate would net the body more utilizable water (via water of oxidation, prevention of ketosis) than would an equivalent weight of water <u>per se</u>, besides providing the morale value of something to eat.

Such a ration might support life for short periods of time, but it was not optimal. A more desirable goal was a ration which could maintain maximal fitness and enable the survivor to cope with his adverse environment until rescue took place, and then he could recover more quickly and completely. Such an objective might be attained by the inclusion of protein in the ration, to spare and replenish bodily tissues. This would be a boon to men suffering from injury,

burns, loss of blood, or shock. In addition, protein could increase the palatability and acceptability of the ration, ever an important factor, since an uneaten ration is worthless.

The chief stumbling block to incorporating protein in a survival ration has always been the classic physiologic concept that protein fed at low caloric levels would perforce be burned for energy. Since the nitrogenous end products of protein thus metabolized require additional urinary water for excretion, it would certainly be uneconomical and hazardous to feed protein when the intake of water is limited.

This objection might be overcome if a protein were found which, perhaps under special conditions, would be retained and used by the body to promote positive nitrogen balance, rather than be metabolized for energy and excreted.

Little progress was made until Gelman focused attention upon the work of Swanson. She had demonstrated that, unlike other proteins, egg albumen unexpectedly promoted nitrogen utilization and decreased urinary nitrogen excretion in rats fed at subnormal caloric levels, provided 50% of the minimal theoretical basal caloric requirements were met. (1) Swanson also found that supplementation with the essential amino acid methionine promoted nitrogen utilization at even lower caloric levels. These findings were confirmed by Allison in dogs. (2)

Our work with human beings was expanded on the basis of these findings. As the studies progressed, it soon became clear that results obtained in animal experimentation, although indispensible, could not always be directly transferred to human beings (e.g. caloric requirements, methionine supplementation), perhaps because of differences in species. It also became evident that many questions remained to be answered in fundamental human physiology before a perfect ration could be fashioned.

 Continued

From a study of 261 human volunteers tested on 62 different experimental diets, it has become apparent that protein can be included in a survival ration without detrimental effect, even when the intake of water is limited to 800 cc. daily. More important is the fact that such inclusion of protein is actually beneficial, since it promotes nitrogen utilization and preservation of the bodily tissues.

It has been found that the effectiveness of ingested protein is especially influenced by a number of factors:

1. Caloric Level - Little or no nitrogen is retained at the 400-500 calorie level. When 3.0 grams of protein nitrogen are fed, the level must be raised to 1500-1800 calories befores significant utilization occurs.

2. Quantity of Protein - If the quantity of protein nitrogen fed is increased to 6.0 grams, a caloric level of 900 is sufficient to promote utilization. This factor is apparently resident in the increased amount of protein *per se*.

3. Quality of Protein - The biological value or efficiency of a protein determines its ability to be retained by the bodily tissues. In our studies, egg albumen was found superior to one brand of lactalbumen and to protein derived from malted milk. It was also somewhat preferable to whole egg.

4. Quantity of Fat - An increase of the content of fat in the diet to 30% by weight promotes a utilization of nitrogen not found with lower amounts. This phenomenon is unrelated to the caloric content of the fat.

5. Quantity of Salt - The inclusion of as little as 1.0 gram of salt in the daily ration improves nitrogen metabolism and appears to aid renal function. Exclusion of salt produces both clinical and laboratory evidence of salt deficiency, with possibly a role played by the adrenal cortex.

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6. Quantity of Water - Limitation of water to 800 cc. daily produces no significant physiologic disturbances. Contrariwise, allowance of an ad libitum intake of water produces a more negative nitrogen balance. This phenomenon is apparently mediated in the tissues, and is not dependent upon diminished renal or hepatic function.

7. Methionine - Unlike its effect in animals, d-l methionine supplementation not only does not improve nitrogen utilization, but actually diminishes it somewhat. This occurs at both the 900 and 1800 calorie levels, with and without protein in the diet. The phenomenon may well represent a species difference, or perhaps depend upon variations in the quantities of the amino acid used.

8. Periodicity of Feeding - Periodicity of feeding produced no alteration in utilization of nitrogen at 900 calories, but indicated a slight tendency toward improvement at 1200 calories when the total daily ration was fed at one time.

9. Increased Caloric Output - With a forced daily output of 600 and 1500 calories, respectively, beyond the energy expenditure of semi-ambulation, no decrease was noted in nitrogen retention. This may have been associated with hypertrophy of muscular fibers from exercise.

It has also become apparent that, based upon the above principles, a ration can be fashioned which not only will support survival, but maintain subjects in relatively good condition for several weeks. Such a ration might contain 900-1000 calories, 45-50 grams dried egg albumen (providing 6.0 - 7.0 grams nitrogen), 30% hydrogenated fat by weight, and the remainder carbohydrate. One gram of salt per day should be assured, and the intake of water kept to about 800 cc.

Such a ration would be of value for a general survival ration, usable by all the branches of the armed forces. It could be used in multiples of a basic unit, thus being adaptable to different climates and different caloric requirements indigenous to them.

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Survival-type rations of the sort herein suggested could be easily adapted to the feeding of segments of the civilian population (frequently enough a military responsibility) both here and abroad, either during hostilities or during a post-war period. The investigations presently reported emphasize that less stress should be laid on the absolute quantity and caloric content of food in the daily allowances than upon the intrinsic composition of that food in terms of proteins, fats, and adjuvants.

The physiologic principles evolved in these studies have an obviously direct bearing on various phases of medical and surgical care where there is either an involuntary or a mandatory disturbance of normal alimentation or fluid balance. This includes preoperative and post-operative surgical care, weight reduction, or any situation where destruction of bodily tissues is taking place.

Without question, much more work remains to be done. Some of the more pressing problems that should be further investigated include:

1. The values of additional types of protein and of mixtures of various types.

2. The effects of various mixtures of amino acids.

3. The apparently deleterious effect of large amounts of fluid intake upon nitrogen utilization.

4. The part played by the steroid hormones and electrolytes in nitrogen metabolism.

5. The effects of greatly increased outputs of energy upon nitrogen metabolism.

It is to be stressed that such investigations be continued on the basis of close liaison between groups working with animals and those employing human subjects, since they are not mutually exclusive and since neither can do a complete job alone. It may not be amiss to reemphasize that basic physiologic research, though perhaps not answering an immediate practical military question, is vital to answer those likely to come up in the near future.

Finally, the suggestion is respectfully offered that such research be set up wherever possible on a continuing basis, so that interruptions and losses of time may not occur because of impending uncertainties of continued financial support.

BODY OF REPORT

As indicated in the General Summary, the primary aims of this investigation have been to study the physiology of low caloric feeding, particularly with reference to the metabolism of protein utilization in human beings.

It will become clear that the overall program was not and could not have been mapped in detail at the start because of the paucity of available information. Rather, the successive experiments were planned and executed on the basis of results and questions deriving from the immediately preceding studies by us and by kindred groups working under the direction of the Quartermaster Food and Container Institute.

This portion of the report will consist of the following sections:

I. Methods and Materials

II. Factors Influencing Protein Metabolism

- A. Caloric Level
- B. Quantity of Protein
- C. Quality of Protein
- D. Quantity of Fat
- E. Quantity of Salt
- F. Quantity of Water
- G. Methionine
- H. Periodicity of Feeding
- I. Increased Caloric Output

III. Miscellaneous Observations

- A. Urinary Ketosteroids
- B. Circulation Times
- C. Blood Sugar

IV. Publications

V. Bibliography

In cases where any of these topics have already been reported in detail, references will be given, and only a summary of the findings offered.

METHODS AND MATERIALS

From the initiation of these studies in February, 1945, to their cessation in May, 1948, comprehensive observations have been made on an integrated series of 62 different experimental dietary regimens, variously providing 400 to 1800 calories, 0% to 30% protein (providing 0 - 6.00 grams nitrogen), and 0% to 30% hydrogenated fat. The exact compositions of these diets is listed in Table I.

Two hundred fifty one healthy adult human volunteers were used as subjects in these experiments. During the first two years, these consisted of Conscientious Objectors obtained through the cooperation of the American Friends Service Committee in Philadelphia; thereafter, the volunteers were selected from Quartermaster Corps Enlisted Men at Camp Lee, Virginia, and the Third Armored Division at Fort Knox, Kentucky. Their ages ranged from 17 to 40 years, and their weights from 52 to 93 kilograms.

These men were considered to be in good health. All had passed Army Induction Physical examinations before assignment either to Civilian Public Service camps in the case of the Conscientious Objectors, or to regular Army units in the case of the Enlisted Men. In addition, preliminary to his use as a test subject, the physical status of each was thoroughly checked by a careful history, physical examination, electrocardiogram, chest roentgenogram, blood count, urinalysis, erythrocyte sedimentation rate, blood sugar, and urea nitrogen.

Because of the potentially wide variations in normal human physiological responses, the paired-run technique was utilized throughout. With this method, a basic control group was always run in parallel with other groups subjected to the specific dietary variations under observation. Each dietary test group consisted of four to six men, and a total of ten to twenty subjects were studied during each experimental run. Table II lists the twenty experimental runs, their date of initiation, and the total number of men employed as subjects.

Continued

TABLE I

Diet No.	Daily Calories	Percent by Weight Carbo.	Fat	Protein	Grams Nitrogen	plus or minus
1	400	100	0	0	—	0.10
2	400	90	0	10	1.2	0.10
3	400	80	0	20	2.4	0.10
4	513	65	25	10	1.2	0.10
5	400	100	0	0	—	
6	450	86	10	4	0.5	0.05
7	450	90	10	0	—	
8	450	78	10	12	1.6	0.10
9	850	90	10	0	—	
10	850	80	10	10	3.0	0.15
11	800	90	10	0	—	
12	800	80	10	10	3.0	0.15
13	900	90	10	0	—	
14	900	80	10	10	3.0	0,15
15	900	60	10	30	7.7	0.10
16	900	90	10	0	—	
17	900	90	10	0	0.47 meth.N	
18	900	70	10	20	6.0	0.15
19	900	80	10	10	3.0	0.15
20	1200	82.5	10	7.5	3.0	0.15
21	1800	83	10	5	3.0	0.15
22	1800	80	10	10	6.0	0.15
23	1800	80	10	10	6.0	0.15
					+0.23 meth. N	
24	1800	85	10	5	3.0	0.15
					+0.23 meth. N	
25	1200	82.5	10	7.5	3.0	0.15
26	1500	84	10	6	3.0	0.15
27	1200	75	10	15	6.0	0.15
28	1500	78	10	12	6.0	0.15

(continued)

TABLE I (continued)

Diet No.	Daily Calories	Per cent by Weight Carbo.	Fat	Protein	Grams Nitrogen	plus or minus
29	450	80	10	10	2.62	0.15
30	450	80	10	10	2.62	0.15
31	450	80	10	10	2.62	0.15
32	900	80	10	10	2.72	0.15
33	900	80	10	10	2.72	0.15
34	900	80	10	10	2.72	0.15
35	900	80	10	10	3.20	0.10
36	900	70	20	10	2.89	0.10
37	900	60	30	10	2.84	0.10
38	1200	80	10	10	3.48	0.15
39	1200	80	10	10	3.48	0.15
40	1200	80	10	10	3.72	0.15
41	1800	72.5	15	12.5	6.57	0.10
42	900	45	30	25	5.42	0.10
43	1800	72.5	15	12.5	6.57	0.10
44	900	45	30	25	3.28	0.10
45	900	45	30	25	6.20	0.15
46	900	67.5	30	12.5	3.00	0.15
47	1800	72.5	15	12.5	6.20	0.15
48	1800	72.5	15	12.5	6.20	0.15
49	900	45	41	14	6.00	0.10
50	900	45	30	25	6.00	0.10
51	900	70	30	0	0.00	----
52	900	45	30	25	6.00	0.10
53	900	45	30	25	6.00	0.10
54	900	45	30	25	6.00	0.10
55	900	45	30	25	6.00	0.10
56	900	45	30	25	6.00	0.10
57	900	70	30	0	0.00	----
58	900	45	30	25	6.44	0.15
59	900	45	30	25	6.44	0.15
60	900	45	30	25	6.54	0.15
61	900	45	30	25	6.54	0.15
62	900	70	30	0	0.00	----

Continued

TABLE II

GROUPING OF EXPERIMENTS

Diet Numbers	Number of Subjects	Date Initiated
1 - 5	10	February, 1945
6 - 8	10	March
9 -10	10	August
11-12	10	September
13-15	12	November
16-18	12	December
19-21	12	January, 1946
22-24	12	February
25-26	11	March
27-28	11	May
29-31	11	September
32-34	12	October
35-37	12	January, 1947
38-40	13	February
41-44	16	March
45-48	16	May
49-51	14	September
52-54	16	December
55-57	11	February, 1948
58-62	20	April

The basic pattern for each experimental run has included three successive periods:

1. Standardization period - five to ten days

2. Testing or "Deprivation" period - five days for Diets 1-5, inclusive; ten days for Diets 6-48, inclusive; forty days for Diets 49-51, inclusive; fifteen days for Diets 52-54, inclusive; twenty days for Diets 55-57, inclusive; and thirty-five days for Diets 58-62, inclusive

3. Recovery period - five days

During the standardization period, the men ate full Army 10-in-1 Rations, and drank water ad libitum. During this phase, control levels were established for the clinical and laboratory tests to be repeated in the deprivation and recovery periods.

In the deprivation period, the subjects ate the experimental ration in four installments, at 9 A.M., 1 P.M., 5 P.M., and 9 P.M. The only exception to this procedure was followed with Diets 32-34, inclusive, and Diets 38-40, inclusive, where the effects of periodicity of feeding were being studied, and varied schedules were employed (see later). One fourth of the daily 800 cc. ration of water was drunk with each of the standard feedings, except on those specific Diets where the specific effects of water ad libitum were being investigated (Diets 30, 50, 52, 55, 59, 61, and 62).

During the recovery period, the men were again fed the 10-in-1 Ration. On the first recovery day, they were limited to 1200 calories of food if the experimental diet had provided 900 calories or less, and 2500 cc. water, to prevent gastro-intestinal upsets. Thereafter, calories and water were permitted to be taken ad libitum.

All food and fluid were carefully weighed, measured, checked, and charted by the dietitian in charge. This included the reweighing of food already packaged and labelled for weight.

Except for the first eight diets, which were packeted in a compressed confection form, all the experimental rations were in the form of biscuits. The latter were specially baked for these experiments in accordance with proferred formulas. The ingredients were weighed out on a dry as-is basis, then water was added and the materials thoroughly mixed. Baking was carried out at 360' F. until very slight surface browning appeared. After drying, each sample was analyzed for moisture content, with the range being 3-12%. With each ration, calculations were made of the total weight required to provide the requisite amount of calories and nitrogen for the individual experiments. The nitrogen content of each sample was determined by direct Kjeldahl analysis of pulverized biscuits. The amount of moisture present in each subject's daily quota of biscuits was deducted from his daily allotment of water. It may be mentioned that no attempt was made to make these biscuits tempting, either in taste or appearance.

The experimental rations were baked in cooperation with the the Institute by the Sunshine Biscuit Company, the National Biscuit Company, the Gottfried Baking Company, and the Ward Baking Company, with the Sunshine firm responsible for the great majority.

The subjects were confined during these experiments as regular patients to Ward K of the New York Medical College, Metropolitan Hospital Research Unit. They were allowed to be ambulatory on the premises, but at no time did they leave the ward without supervision. They rested or slept whenever they wished during the day, except for feeding and testing times; at night they were in bed by 11 O'clock. Records were kept of the quantity and quality of sleep.

Many laboratory determinations on both blood and urine, as well as general tests of bodily function were performed almost daily throughout the experiments. Twenty-four hour urinary collections were made from 8 A.M. of one day to 8 A.M. of the next day. Fasting samples of venous blood were drawn between 8:00 and 8:30 A.M., preceding the first morning feeding. Pre-sealed vacuumatic tubes were used to insure against contamination.

A detailed description of laboratory techniques is available in a previous report to the Committee on Food Research (3).

II. Factors Influencing Protein Metabolism

A. Caloric Level - Previously reported (4), with full tables and graphs. These findings can be summarized as follows:

1. Nitrogen sparing is not effected within the 400-500 caloric range of feeding (level of standard life raft ration).

2. Nitrogen utilization is distinctly enhanced by increases in the caloric intake, being optimal at 1500-1800 calories when 3.0 grams nitrogen (derived from dehydrated fermented egg albumen) are fed.

3. An increase in the nitrogen intake per se from 3.0 to 6.0 grams daily produces a striking improvement in nitrogen balance at all levels from 900 to 1800 calories.

4. Urinary volumes are not increased when 3.0 and 6.0 grams of protein nitrogen are fed at 1500-1800 calories, averaging 30-60 cc. less than when no protein is ingested at 450 calories, and 115-145 cc. less than when 1.6 grams are given at 450 calories.

These findings are essentially corroborated with Diets 29-62, inclusive. Quantitative variations can be attributed to variations in individual subjects, and to variations in perspiratory losses of water and salt.

B. Quantity of Protein - An increase in the quantity of protein to about fifty grams, so that 6.0 grams dietary nitrogen are provided, produces a definite improvement in nitrogen balance even at 900 calories (4). However, at the 400-500 level, even small quantities of increase in protein nitrogen impair the utilization, with resultant increases in urinary nitrogen, solutes, and volume.

The beneficial effects of increased amounts of dietary protein are as yet not understood.

C. Quality of Protein - Comparisons have been reported (4) of the value of dehydrated fermented egg albumen, malted milk protein, and lactalbumen. In these

experiments, the egg albumen was found to be distinctly superior to the others in promoting nitrogen utilization. Further comparison with other preparations of lactalbumen would seem desirable, however, since the batch used had an unduly high ash content.

The effectiveness of dehydrated egg albumen and whole egg was compared in three sets of experiments: Diets 42 and 44; 53 and 54; and 58 and 60. All were conducted at the 900 caloric level, with the intake of water limited to 800 cc. The data from Diets 53 and 54 were discarded because the subjects were considered unreliable.

Diets 42 and 44 were tested for ten days. Diets 58 and 60 were projected for 35 days, but a rapidly diminishing acceptability of Diet 60 (containing whole egg) forced termination of that diet on the 18th day of deprivation.

The composition of these several diets is given in Table III. It will be noted that Diet 44 contained 41% fat and only 14% protein. This was occasioned by the mistaken notion that the whole egg powder had been defatted, wherefore the baking mixture was weighed out to contain 25% whole egg, 30% hydrogenated fat, and 45% carbohydrate.

TABLE III

Comparison of Egg Albumen and Whole Egg

Diet	Carb.%	Fat%	Protein%	Type Protein	Gm. Nitrogen
42	45	30	25	Egg Alb.	5.42
44	45	41	14	Whole Egg	3.28
58	45	30	25	Egg Alb.	6.44
60	45	30	25	Whole Egg	6.54

In the first experiment (Diets 42 and 44), the egg albumen performed better: total urinary nitrogen was 6.00 grams versus 7.24 for whole egg; nitrogen balance - 0.55 grams versus - 3.95; urinary volume 361 cc. versus 394; urinary solutes 348 milliosmols versus 364; and loss of weight 3.2 kg. versus 4.1. This might be considered to have been due to the increased amount of protein nitrogen

in the egg albumen diet. With diets 58 and 60, where the nitrogen contents were comparable, the differences were not remarkable except that the group on egg albumen lost only 4.3 kg. as compared with a total of 6.5 kg. for the whole egg group in 15 days.

The nitrogen balances were unduly negative in both cases, the deficit amounting on the average to over 3.0 grams.

It is quite possible that the results obtained may be related to the methods of baking (as also in the case of some other variations) which may have altered the quality, digestibility, or absorbability of the protein. Further comparisons are distinctly necessary between these two types of egg products.

D. Quantity of Fat - The content of hydrogenated fat in Diets 6-34, inclusive, was maintained constant at 10% by weight, as seen in Table I. This amount was used to increase palatability and caloric density. That no serious attempt was made to increase the percentage beyond the 10% figure was due to the occurrence of abdominal cramps, nausea, and flatulence with Diet 3, which contained 25% (approximately 25 grams).

When the progressing studies indicated the need for increasing the caloric intake to produce nitrogen utilization, the potential weights required threatened to exceed by far the limits of weight and space set by the Air Corps. Therefore the question of raising the fat level was again considered, in order to increase the caloric density. Digestive disturbances were the main fear, and therefore graduated quantities of fat were introduced in amounts of 10%, 20%, and 30%, respectively in the isocaloric Diets 35, 36, and 37 (see Table I).

Each diet was fed for ten days to a group of four men. The four daily feedings supplied a total of 900 calories. Water was limited to 800 cc., with 1.0 gram salt dissolved therein. The significant results are given in Table IV:

TABLE IV

Effect of Varying Quantities of Fat

Diet	% Fat	Gm. T.N. in Urine	Nitr. Bal. Gm.	Urin. Vol. cc.	Urin. Solutes m/osmols
35	10	5.56	-2.26	308	327
36	20	5.69	-2.98	300	345
37	30	4.32	-1.48	225	248

It is apparent that no significant difference exists between the diets containing 10% and 20% fat. However, when the fat content is raised to 30%, a definite improvement is apparent. This beneficial effect cannot be attributed to caloric intake, since the three diets were all isocaloric. It must be associated with some property inherent in the fat itself.

Of practical importance is the fact that no digestive disturbances were encountered even with the 30% regimen. (v. also absence of digestive disturbances with Diet 44, inadvertently made up to contain 41% fat). That untoward symptoms did occur with Diet 3 containing 25% fat can probably be attributed to a "bleeding out" phenomenon.

That the beneficial effects of both the increased fat and protein can work together without detriment, but apparently without additive effect, is indicated by the results obtained with Diet 42. This supplied 5.42 gm. nitrogen and 30% fat, and gave the following results in a ten day test:

Total urinary volume	361 cc.
Total urinary solutes	348 milliosmols
Total urinary nitrogen	6.0 grams
Nitrogen balance	0.55 grams
Loss of weight	3.2 kg.

E. Quantity of Water - As has been previously mentioned, the majority of these experiments were conducted with the intake of water limited to 800 cc., a figure representing

the amount expected to be averaged by a castaway from his three potential sources: rain water, desalination kit, and sun still. This limitation especially was adopted after initial observations revealed that no damage resulted in the ten day experimental runs.

No changes were contemplated until plans were made to test Diets 49, 50, and 51, which were projected to run forty days instead of the customary ten. Because of the fear that progressive dehydration with 800 cc. of water might foreshorten the long-range deprivation period, it was decided to allow water ad libitum with Diet 50, which was identical with Diet 49. Although all data for that experiment were discarded because of dishonesty on the part of some of the enlisted men serving as subjects, there appeared to be a definite impairment of nitrogen utilization in thos taking water ad libitum.

Accordingly, the suggestion here derived was restudied with dependable and closely guarded subjects on Diets 55, 56, and 57, all at the 900 calorie level. (see Table I).

Diet 57 represented a protein-free control group. As can be seen in Figures I - IV, inclusive, the advantage lies with the group taking only 800 cc. water. Loss of weight was 0.53 kg. less than with free intake of water; the nitrogen balance was 0.66 - 1.65 gm. better; total urinary nitrogen excretion averaged 0.82 - 2.1 gm. less; and solutes ranged 25-250 milliosmols less.

Although the general level of nitrogen excretion was higher with all three dietary groups than we had expected, by comparison the 800 cc. group appears more favorable, with a urinary volume little higher than the protein-free regimen. It is of interest to note that the men in the ad libitum group (whose intake ranged from 800 to 2500 cc.) showed a lower urinary nitrogen and solute excretion when their intakes of water were lower. There was no correlation of urinary nitrogen with urinary volume in this group. Since there was no evidence at any time of any renal or hepatic impairment in the group imbibing 800 cc. (just as there was none in previous similar groups) water, it seems fair to consider that the differences in nitrogen excretion represent greater retention by the tissues. A very indirect indication of this may be gleaned from the fact that the total urinary excretion of "17 ketosteroids"

consistently averaged about 5.0 mg. less in the 800 cc. group than in the ad libitum group, running about 6.0 mg. daily. This whole phenomenon of water intake should be further studied, preferably with the ad libitum group forced to drink a minimum of about 2000 cc.

F. Quantity of Salt - Studies of electrolytic patterns have already been detailed (4), and are herewith summarized:

1. Absence of salt in 400-500 calorie diets produced muscular cramps characteristic of clinical salt deficiency.

2. These manifestations were associated with decreases in serum sodium and chlorides, and with rises in serum potassium.

3. That this phenomenon was probably not directly due to adrenal cortical hypofunction was indicated by the low urinary excretions of sodium and chloride, and by higher outputs of potassium.

4. Supplementation of the diet with 1.0 grams salt daily prevented muscular cramps. It also maintained the serum sodium and chloride concentrations normal. Serum potassium concentrations in some cases still rose above normal; this appears to have been a dehydration phenomenon.

5. Serum concentrations of potassium were able to be decreased by increasing the caloric intake; by increasing the nitrogen intake; and by supplementation with d-l methionine.

In order to check on the possible role played by dietary salt in the previously referred to phenomenon of increased nitrogen excretion with large intakes of water, Diets 59 and 61 were run. They were identical in all respects, save that they contained 1.4 and 3.8 grams of salt, respectively. Since there was no appreciable difference in the results of nitrogen excretion, it is concluded that salt plays no direct part in the process.

G. Methionine - Supplementation of the diet with d-l methionine was previously fully reported by us (4), and the conclusions are herewith summarized:

1. Supplementation of 900 and 1800 caloric experimental diets for human beings with 5.0 and 2.5 grams methionine, respectively, produced:

   a. Increased total urinary nitrogen excretion
   b. Increased urinary urea nitrogen excretion
   c. Increased urinary ammonia nitrogen excretion
   d. More markedly negative nitrogen balance
   e. Increased urinary volume
   f. Increased total urinary solute excretion
   g. Increased urinary potassium excretion
   h. Decreased serum potassium concentration

2. Under the conditions of these experiments, supplementation of feedings with d-l methionine not only does not improve nitrogen utilization, but actually impairs it somewhat. Loss of urine water is increased.

3. These considerations indicate that it would be unwise and undesirable to supplement survival rations for human beings with methionine.

H. Periodicity of Feeding - On the suggestion of Chaikoff that nitrogen fed is utilized better within several hours after caloric intake has been high, it was decided to check the effects of feeding the test ration at different intervals. To this end, three groups of four men each were studied with Diets 32, 33, and 34 - identical diets of 900 calories each, supplying 2.6 grams of nitrogen. Group 32 ate the diet in the four daily standard feedings; group 33 received 12 hourly feedings from 9 A.M. to 9 P.M.; and group 34 ate the total ration in a single feeding at 9 A.M.

No significant differences were noted with these various feeding patterns. The data have been previously reported (5). A subsequent experiment (5) with diets 38, 39, and 40 at 1200 calories also showed no statistical differences, although there was perhaps a suggestion that the single feeding might be a bit better than the others. This study should be done at the 1500 and 1800 caloric levels.

 Continued

I. Increased Caloric Output - On the basis of the work of Swenson (1) and Allison (2), it was thought that the feeding of 50% or more of the daily basal caloric requirement would suffice to promote nitrogen retention. Accordingly, we made observations at the 900 and 1200 caloric levels (50%+ of the theoretical daily human basal requirement of 1600-1800 calories). Little retention was noted when 3.0 grams of nitrogen were fed (see above) until the 1500-1800 caloric range had been reached. It seemed then that perhaps the 50% figure should have been calculated on the basis of actual caloric output, since it would be logical to expect that the body would use protein for needed calories.

It was therefore decided to test the effect of increased energy output upon nitrogen retention.

Two groups of four men each were placed on identical 1800 caloric Diets 41 and 43 (see Table I). Water was limited to 800 cc., and the customary 1.0 gram supplement of salt was added. One group was permitted to be ambulatory on the Research Ward as in all previous experiments. The other group was marched twelve miles daily at a rate of four miles per hour. Half the marching was done in the morning and half in the afternoon. The calculated average increase in daily expenditure of energy by the marching group was about 600 calories more than that of the control group.

TABLE V

Effect of Increased Energy Output

Diet No.	Gm. T.N. in	Nitr. Bal. Gm.	Urinary Volume cc	Urinary Sol. M/Osm.
41-exercise	6.15	+0.42	347	356
43-no exercise	5.60	+0.97	302	312

These figures do not indicate any real differences. Therefore another experiment was set up with eight additional men, with the exercising group having an energy expenditure exceeding that of the control group by 1500 calories daily. The diets (47, 48) were similar to 41 and 43 previously used.

Continued

Again there was no significant difference between the two groups. The nitrogen balances were $+0.79$ grams for the exercising group, and $+0.58$ for the ambulatory group. Other data obtained parallelled the nitrogen balances.

The only explanation for this apparent paradox is that the body forcibly and selectively deposited nitrogen in the muscular fibers that were undergoing hypertrophy from the marching exercise.

III. Miscellaneous Observations

A. Urinary Ketosteroids - Because the steroid hormones, especially as they relate to the adrenal cortex, play such an important part under conditions of stress, determinations were made of the urinary neutral "17 - Ketosteroids".

Observations were made chiefly in twelve of the experiments, wherein 48 subjects were employed, with correlations drawn between the ketosteroids, circulating lymphocytes, and the blood sugar.

The total 24 hour urinary 17 ketosteroids decreased significantly during all periods of deprivation. The decrease was distinctly less when water was taken ad libitum than when it was fixed at 800 cc. The number of circulating lymphocytes decreased during deprivation in most cases.

In some instances an inverse relationship existed between the total circulating lymphocytes and the urinary concentration of ketosteroids. No consistent clear-cut relationship was found between the levels for blood sugar and lymphocytes.

It appears that the subnutrition imposed in these experiments does not constitute a condition of acute stress, if urinary ketosteroids can be used as a criterion of such stress.

B. Blood Sugar - The occurrence of symptoms and signs of hypoglycemia during the first and second days of deprivation in one of the early experiments prompted the checking of serial blood sugar levels in subsequent runs.

It was found that the clinical findings paralleled drops in blood sugar concentration following postprandial peaks. This occurred in both the 400-500 and the 900 caloric dietary groups. These clinical manifestations and laboratory correlations came chiefly after the 9 A.M. and 1 P. M. feedings on the first day of deprivation. The severity of the clinical findings depended not on the absolute low level of the blood sugar, but on the rate and degree of fall. It is also of importance that these fluctuations in blood sugar, and their accompanying symptomatology, were much less marked with diets containing protein than in those not containing it.

These observations may be of practical importance in making up survival rations and in recommending how they be eaten - that is, in large infrequent feedings, or in small infrequent ones. It is clear that hypoglycemic manifestations can impair morale greatly. That such manifestations do not occur beyond the first two days of deprivation indicates that the body probably undergoes a process of adaptation.

C. Circulation Time - The influence of limited food and fluid intake upon the circulation has been previously reported, and our findings are herewith summarized:

1. Arm-to-lip and arm-to-leg circulation times were tested by the fluorescein method in 83 men subjected to 23 test diets.
2. Deprivation produced a prolongation of 3 seconds or more in the arm-to-lip time in 21.7% of cases, and of 6 seconds or more in the arm-to-leg times in 30.1%. In 44% of the men exhibiting arm-to-leg time prolongations, there was no significant increase in the arm-to-lip time.
3. Increases in circulation time are favored by 400-500 calorie feedings, though they may occur when the caloric intake is higher. Dehydration may possibly be a factor.
4. Prolongations in circulation time can be correlated with changes in the amplitude and conformation of the T-wave in Lead I of the electrocardiogram.
5. The apparent susceptibility of the legs to impairment of circulation under deprivation conditions should be considered in the pathogenesis of frostbite, trench foot, and immersion foot.

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Articles are in preparation dealing with the various phases discussed in this report.

 Continued

FIGURE 1

URINARY VOLUME

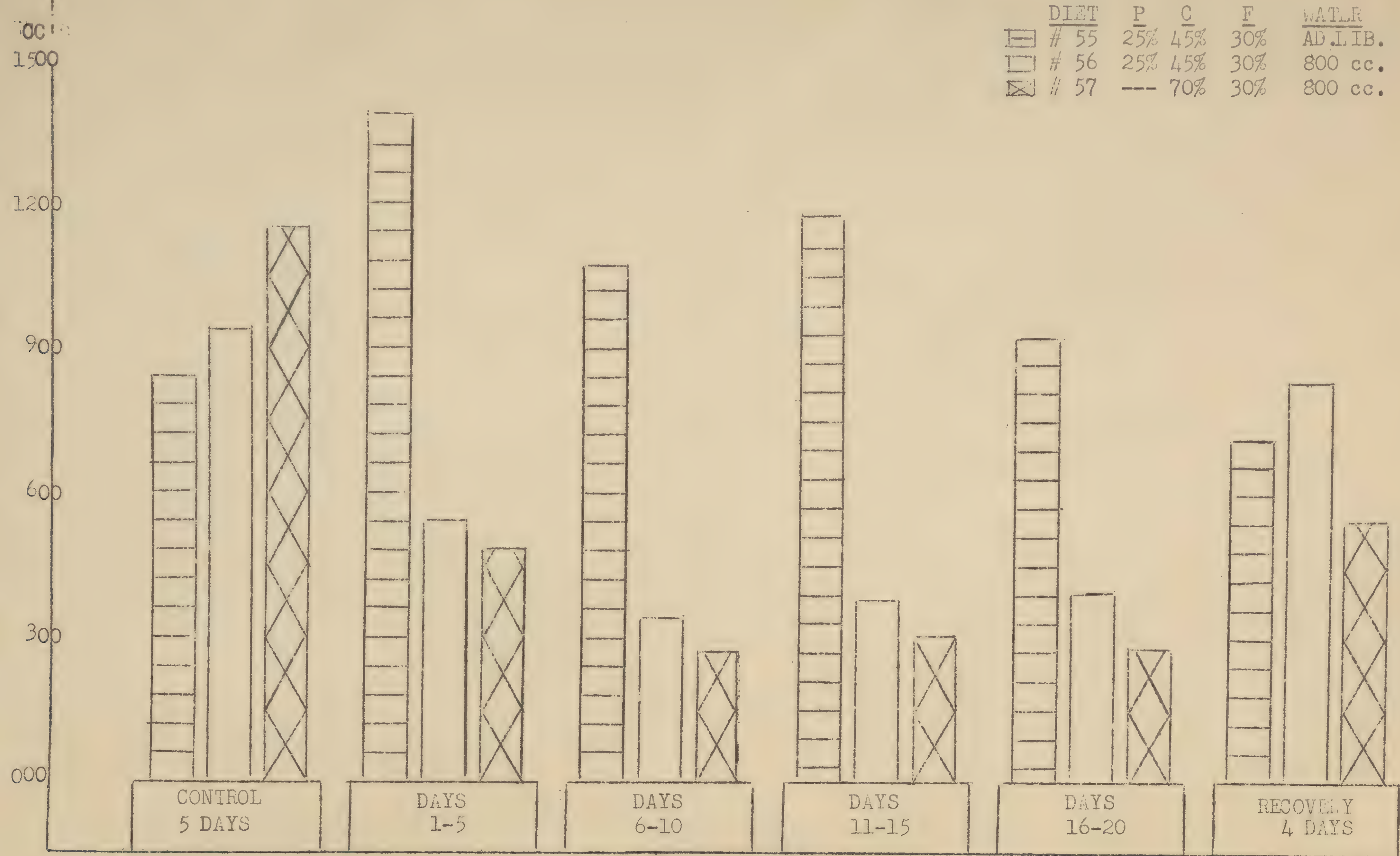

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FIGURE II

TOTAL URINARY SOLUTES

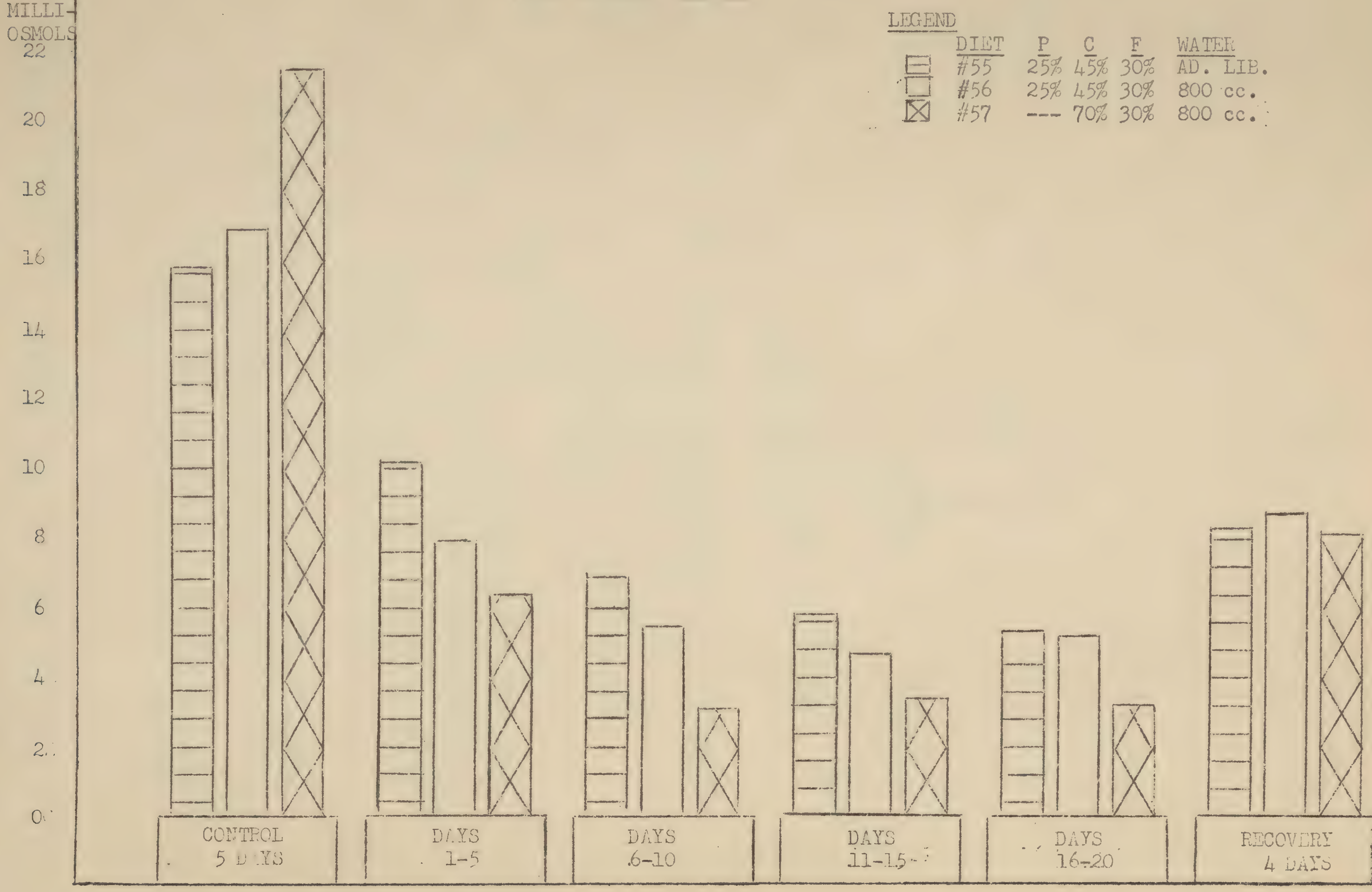

FIGURE III

TOTAL URINARY NITROGEN

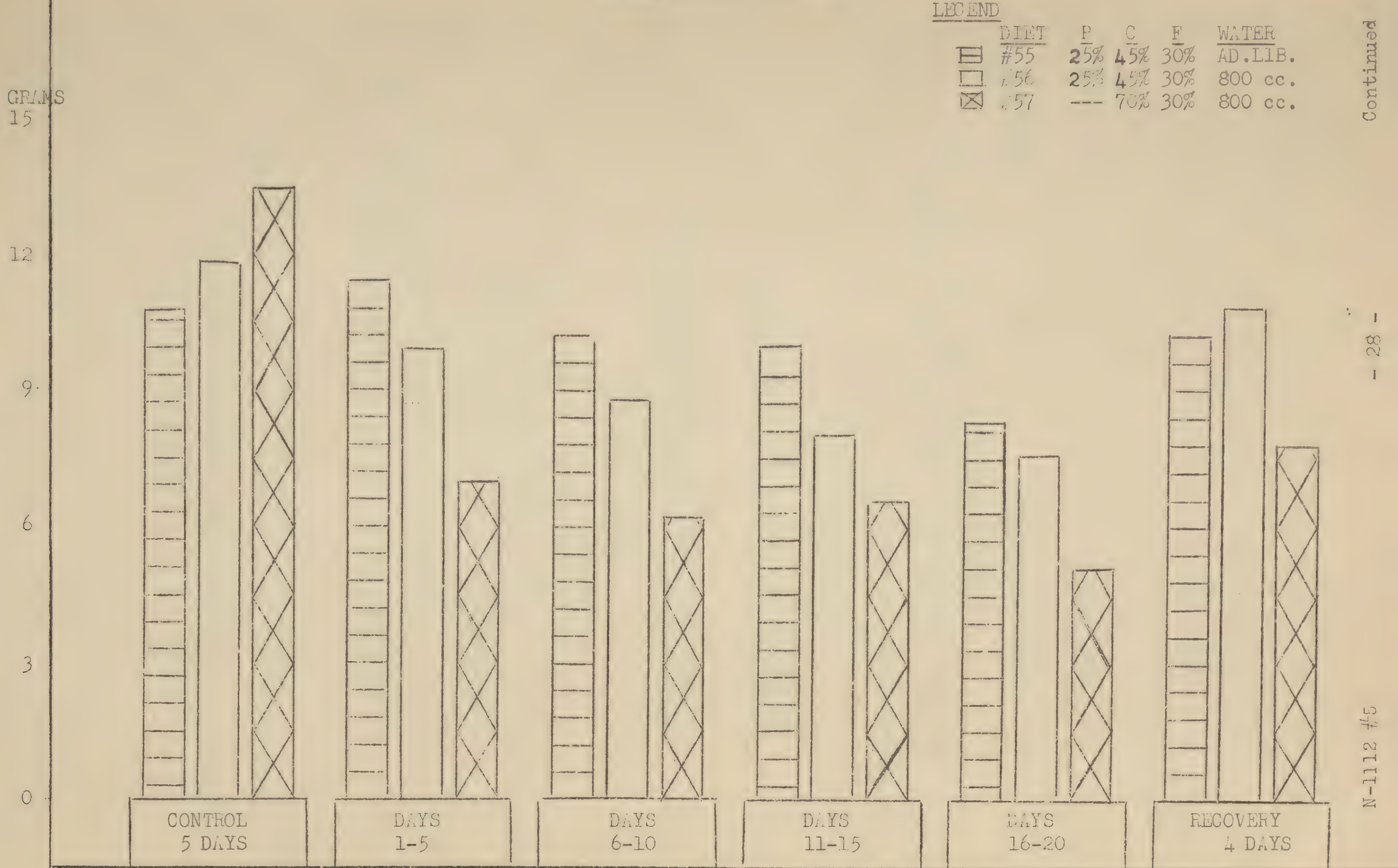

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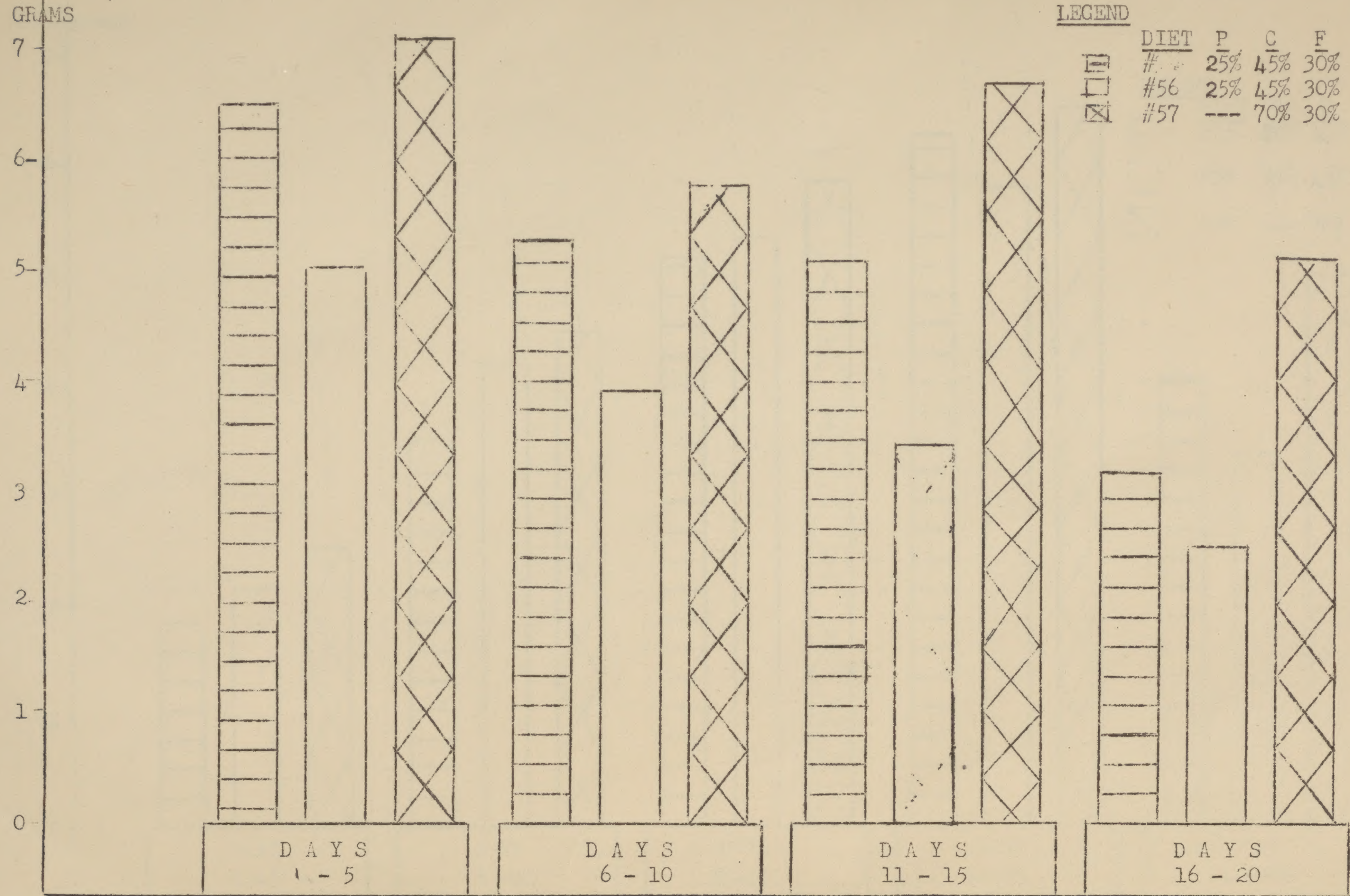
FIGURE IV

NITROGEN BALANCE
(NEGATIVE)



LEGEND

	DIET	P	C	F	WATER
▤	#[illegible]	25%	45%	30%	AD.LIB.
□	#56	25%	45%	30%	800 cc.
⊠	#57	---	70%	30%	800 cc.

Continued

FIGURE V

WEIGHT LOSS